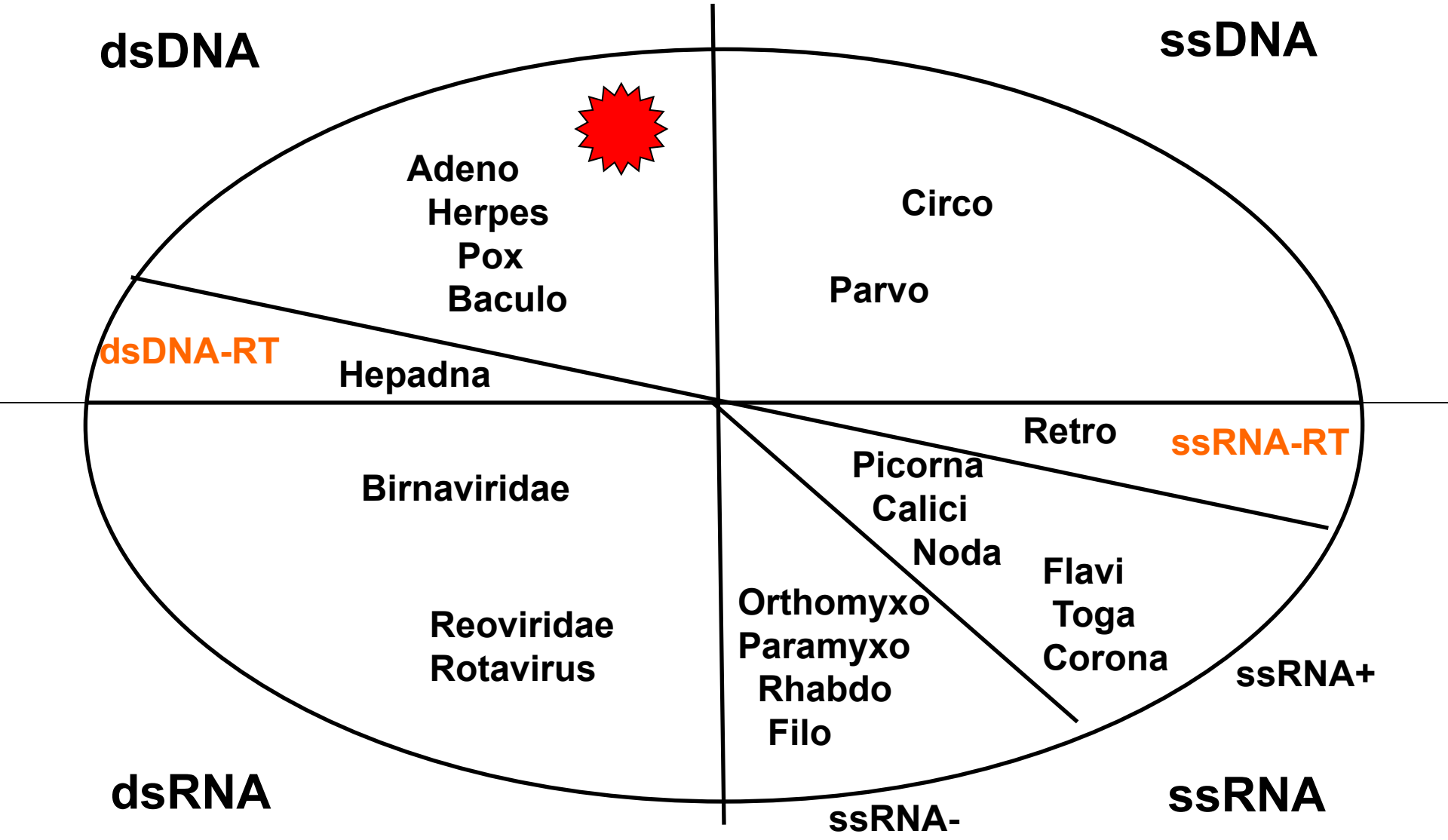
dsDNA viruses

Упрощенная классификация вирусов

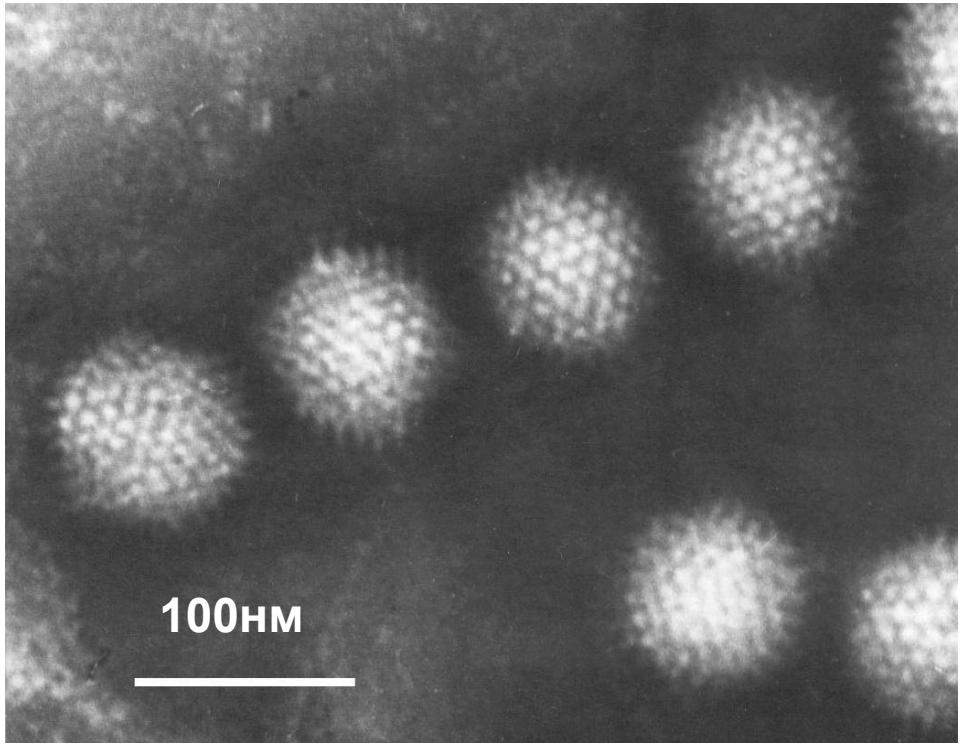


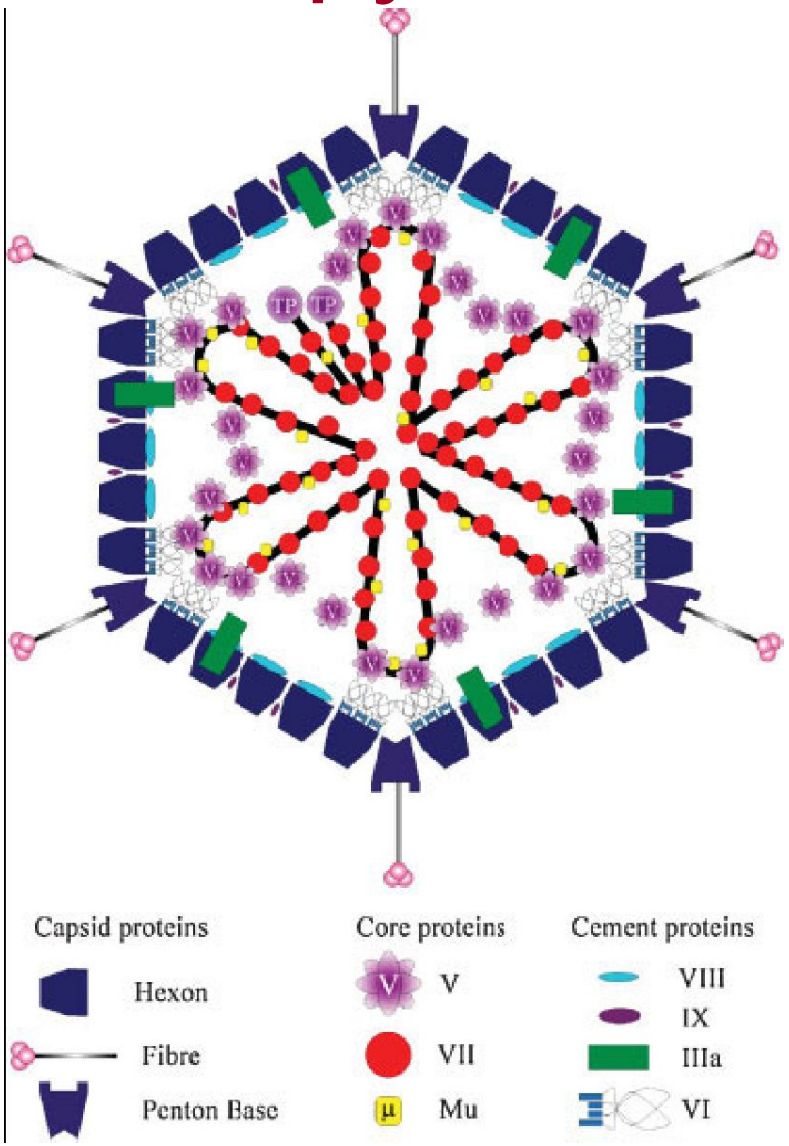
Adenoviridae

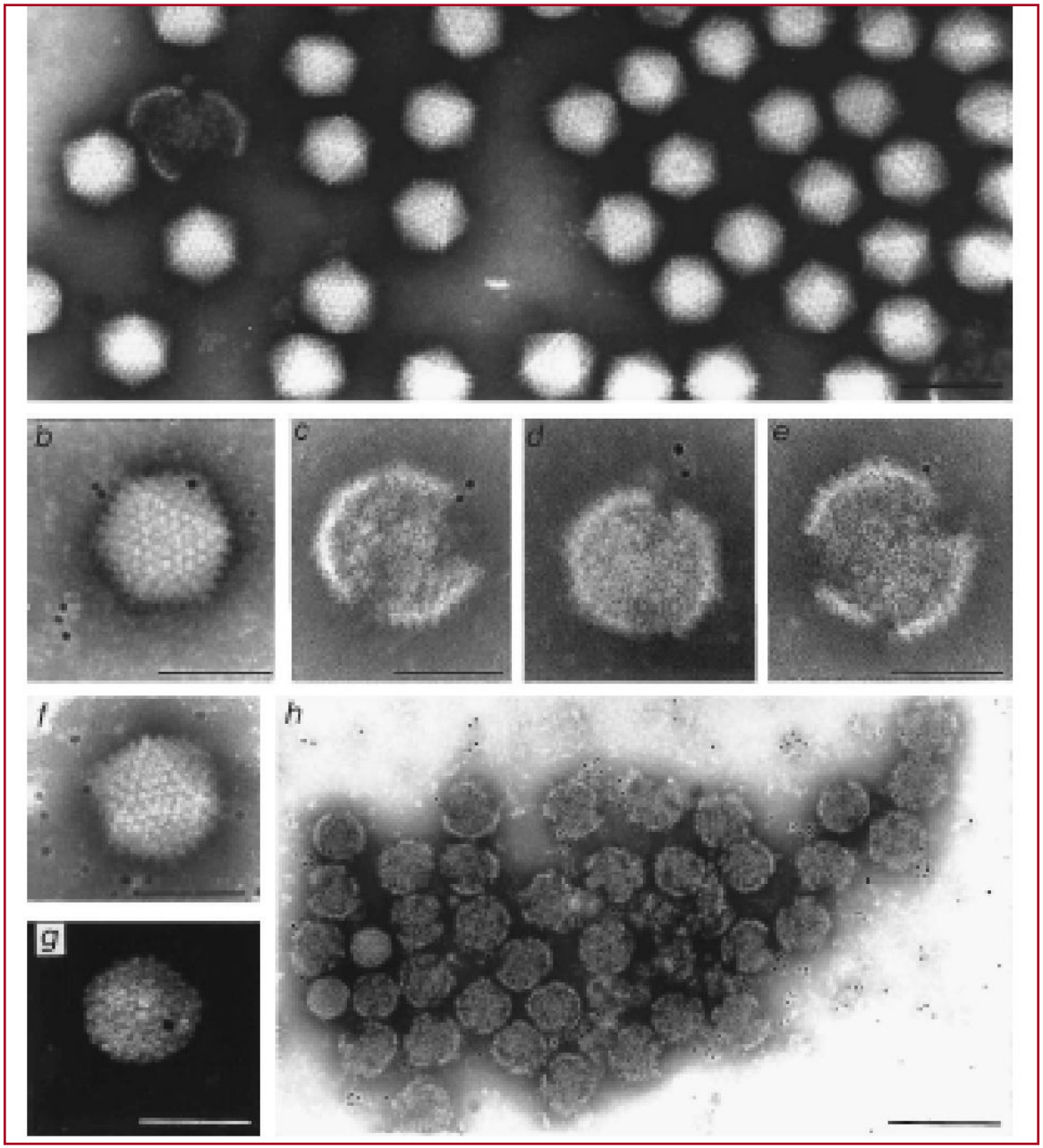
genome - liner dsDNA 30-45kpb

- Atadenovirus. (Овцы, змеи, опоссумы, телята, утки, хамелеоны, ящерицы)
- Aviadenovirus. (Индейки, перепела, цыплята)
- Mastadenovirus. (Млекопитающие)
- Siadenovirus. (Лягушки, змеи)

Строение аденовируса



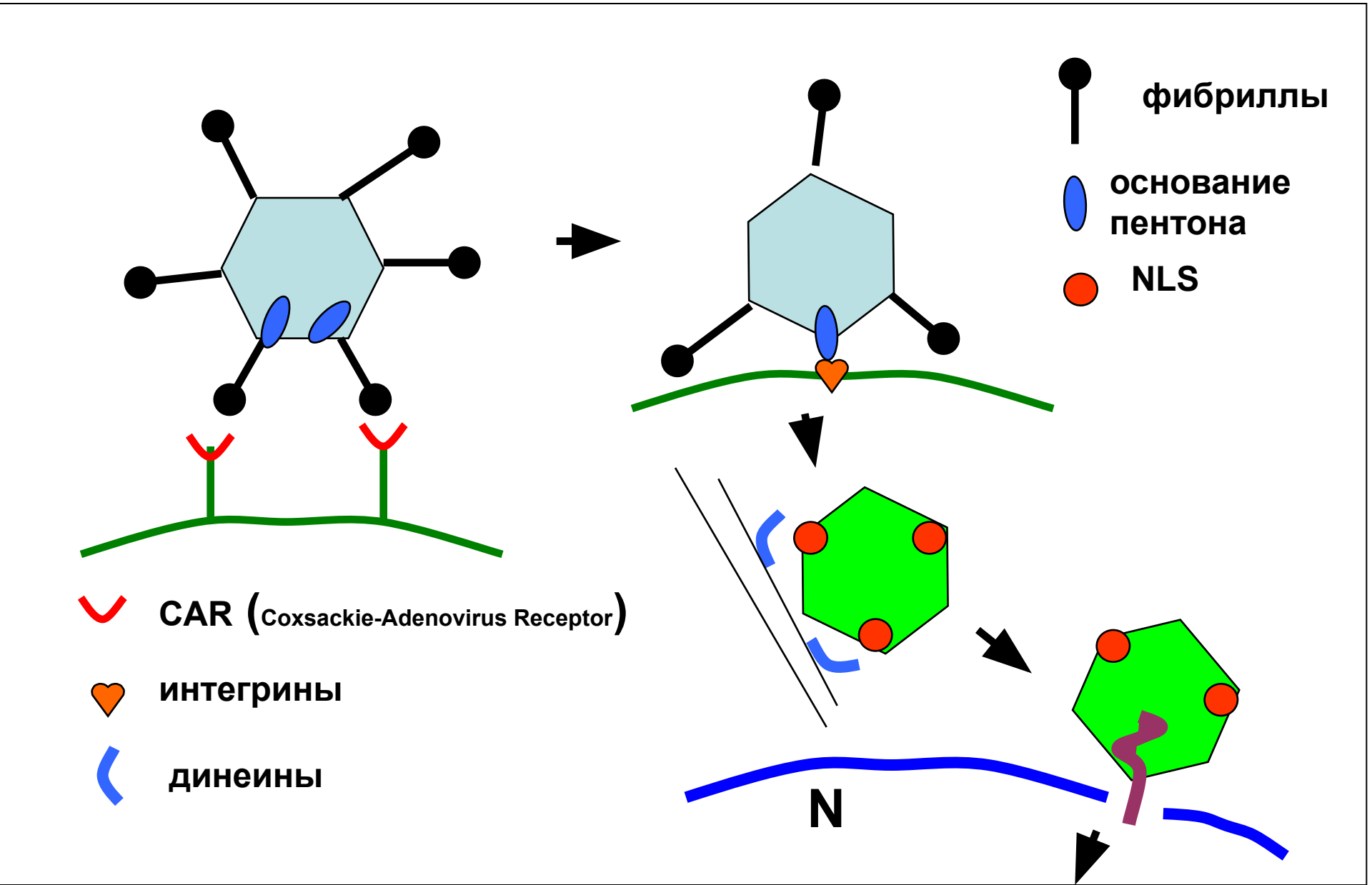


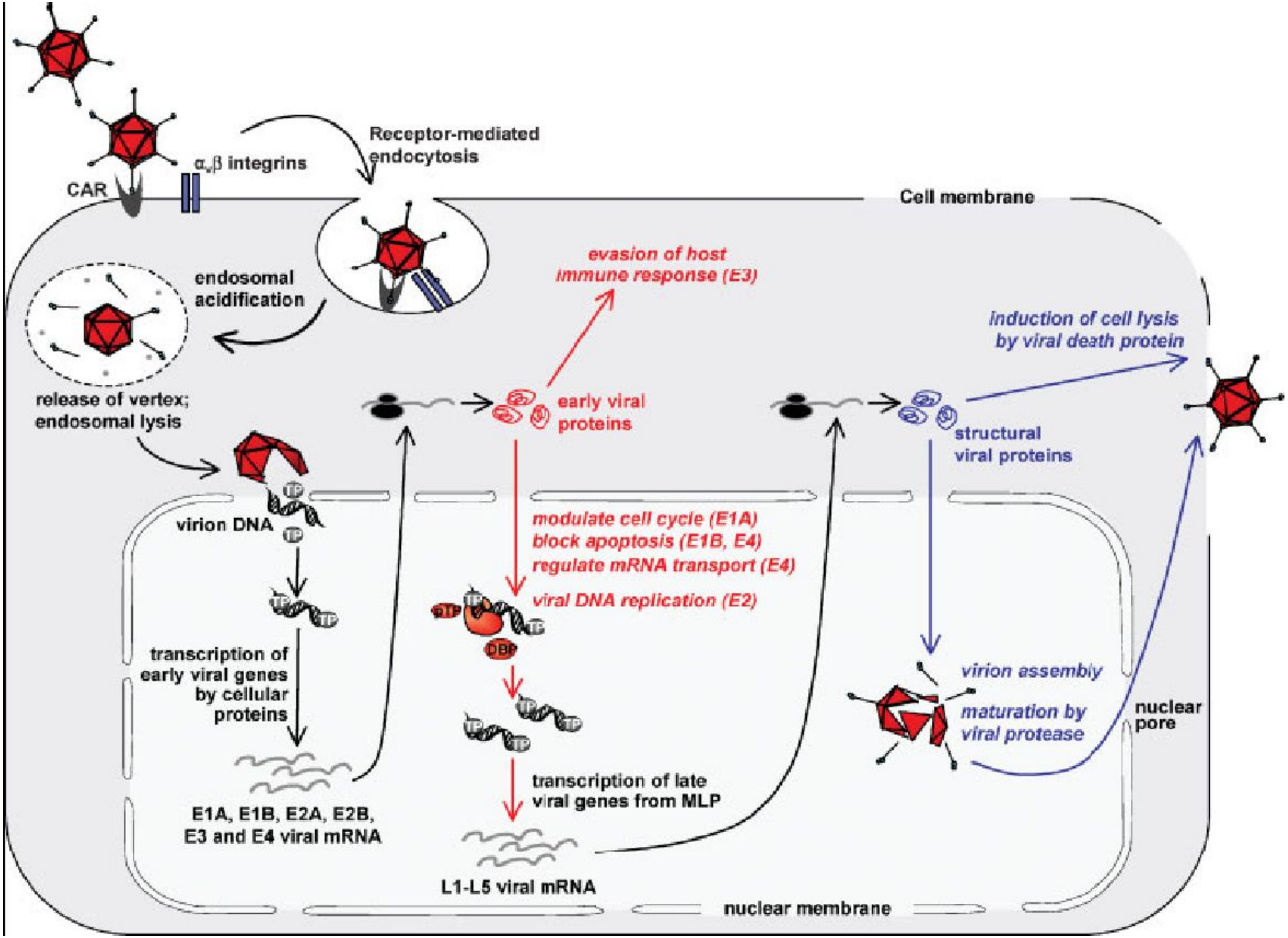


Разрушение аденовируса антителами к белку основания пентона

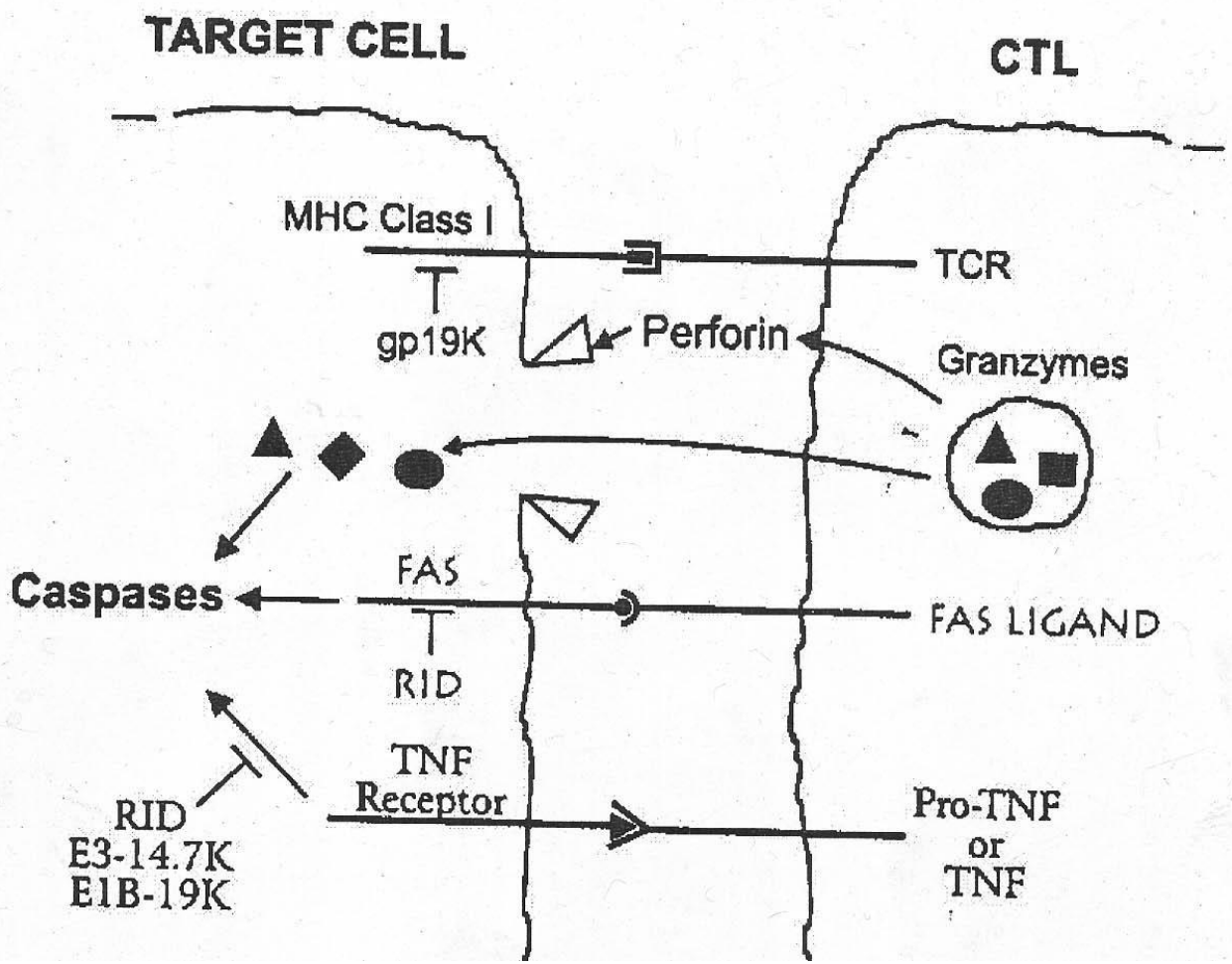
VIRAL IMMUNOLOGY
Volume 13, Number 3, 2000

Проникновение аденовирусов в клетки

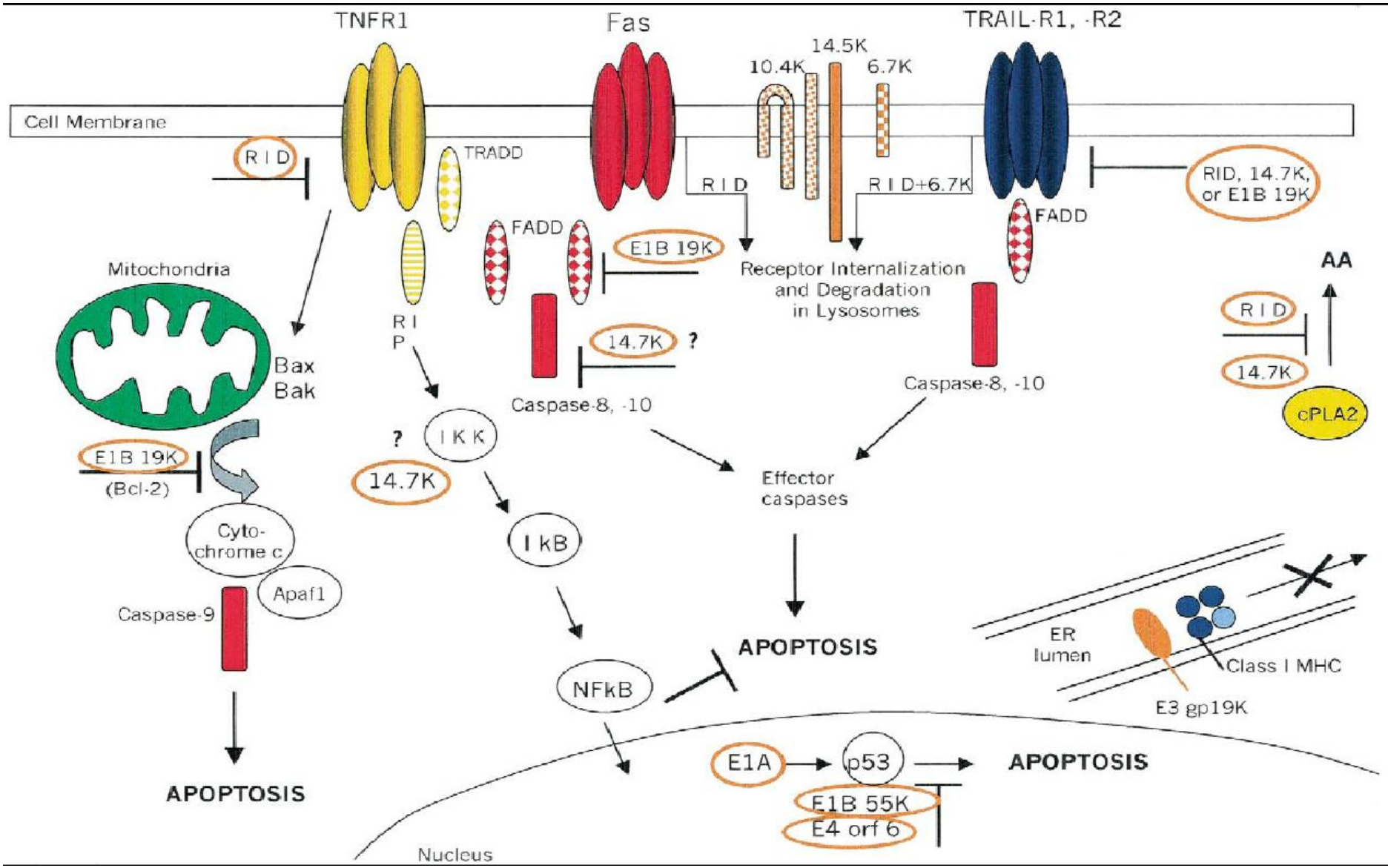



Receptor-mediated endocytosis
$\alpha_v\beta$ integrins
CAR
Cell membrane
endosomal acidification
release of vertex; endosomal lysis
evasion of host immune response (E3)
induction of cell lysis by viral death protein
early viral proteins
structural viral proteins
virion DNA
TP
modulate cell cycle (E1A)
block apoptosis (E1B, E4)
regulate mRNA transport (E4)
viral DNA replication (E2)
pTP
DBP
transcription of early viral genes by cellular proteins
virion assembly
maturation by viral protease
nuclear pore
transcription of late viral genes from MLP
E1A, E1B, E2A, E2B, E3 and E4 viral mRNA
L1-L5 viral mRNA
nuclear membrane

Proposed role for Ad E3 porteins in preventing killing of Ad infected cells by CTL.



Белки аденовирусов блокируют сигналы апоптоза



Herpesvirales

Alloherpesviridae

Вирусы рыб и лягушек

Malacoherpesviridae

Вирусы моллюсков

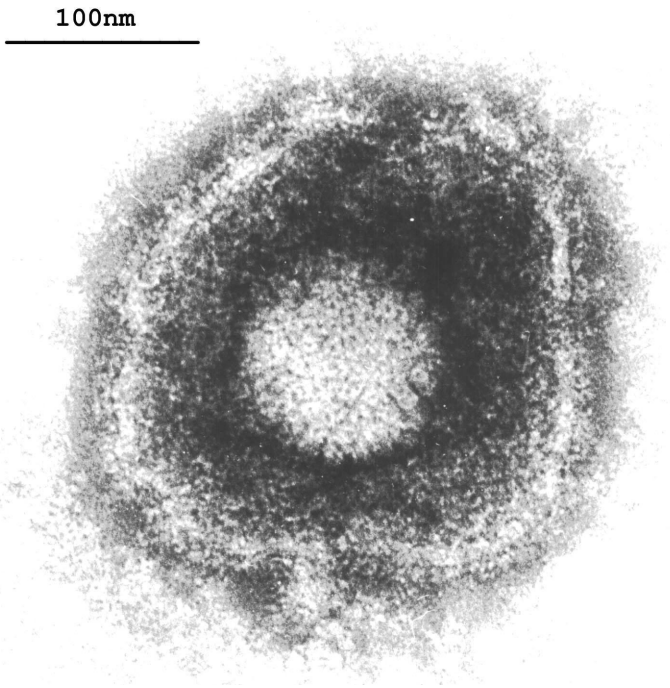
Herpesviridae

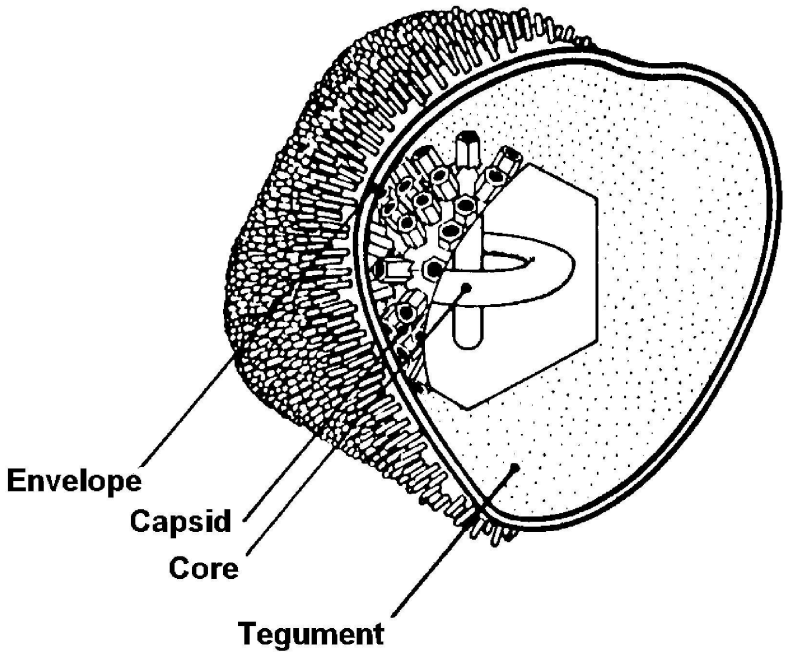
Alphaherpesvirineae

Betaherpesvirineae

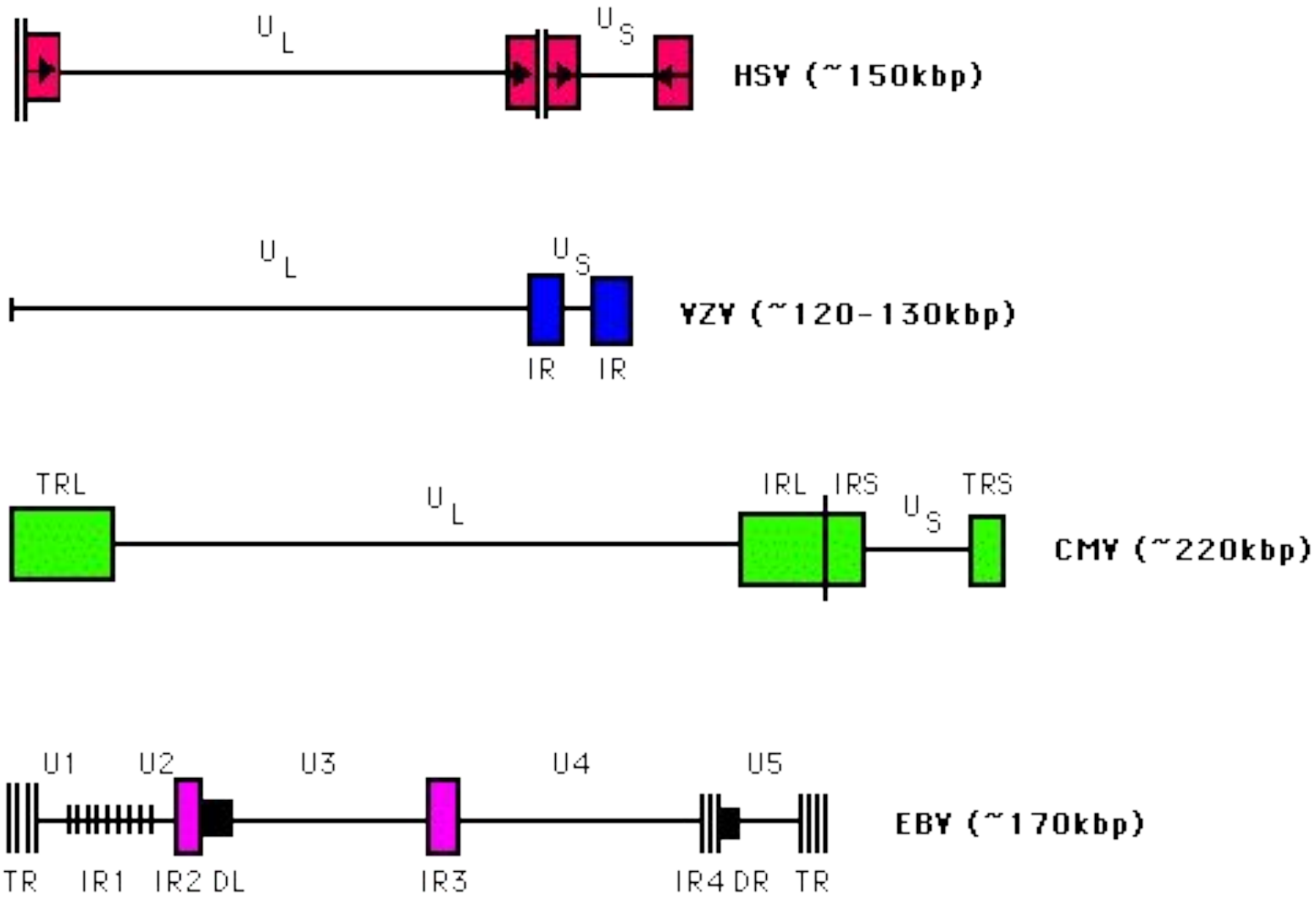
Gammaherpesvirineae

Строение вирионов герпесвирусов



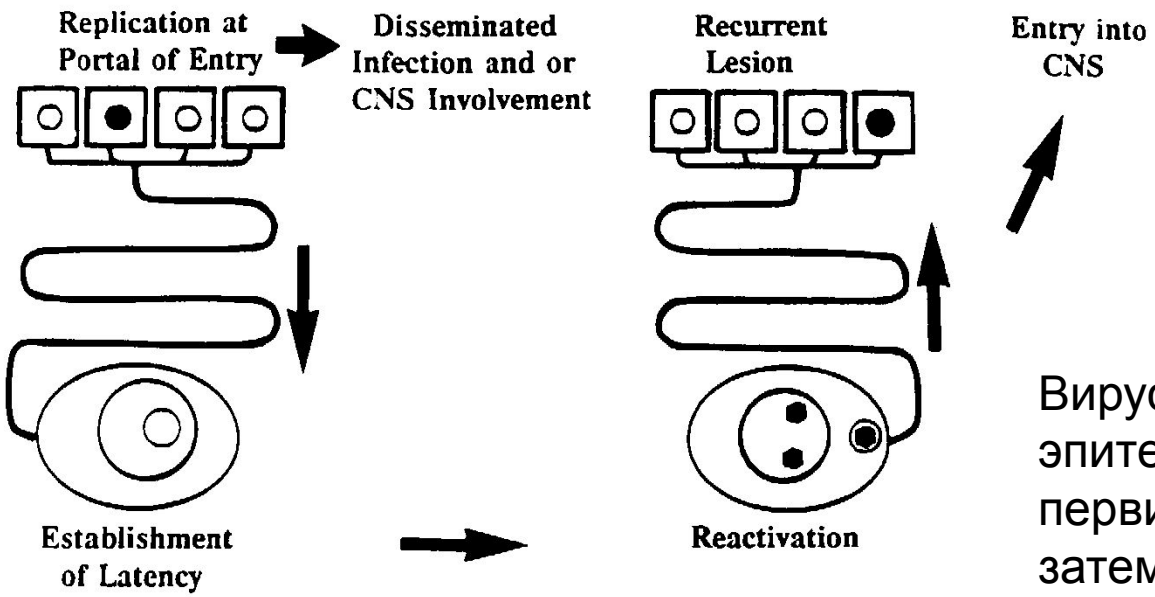


Геном герпесвирусов



	Вид, род	Тропизм	Заболевания
α	***Human herpesvirus 1*** **HHV-1** **(Вирус простого герпеса)** ***Simplexvirus***	**Эпителиальные, латентная инфекция сенсорных ганглиев, ЦНС**	**Высыпания на слизистых**
α	**HHV-3 Varicella-Zoster** ***Varicellovirus***		**Ветрянка, опоясывающий лишай**
β	**HHV-5 CMV** ***Cytomegalovirus***	**Эпителиальные, Моноциты, макрофаги**	**Внутриутробная инфекция**
β	**HHV-6** ***Roseolovirus***	**Моноциты, Т-лимфоциты**	**Краснуха, ложная краснуха (roseola infantum)**
γ	**HHV-4 EBV** (Эпштейн-Барр вирус) ***Limphocryptovirus***	**Эпителиальные, В-лимфоциты**	**Мононункеоз, Лимфома Беркитта онкогенез**
γ	**HHV-8** ***Rhadinovirus***		**Саркома Капоши у иммунодефицитных больных**

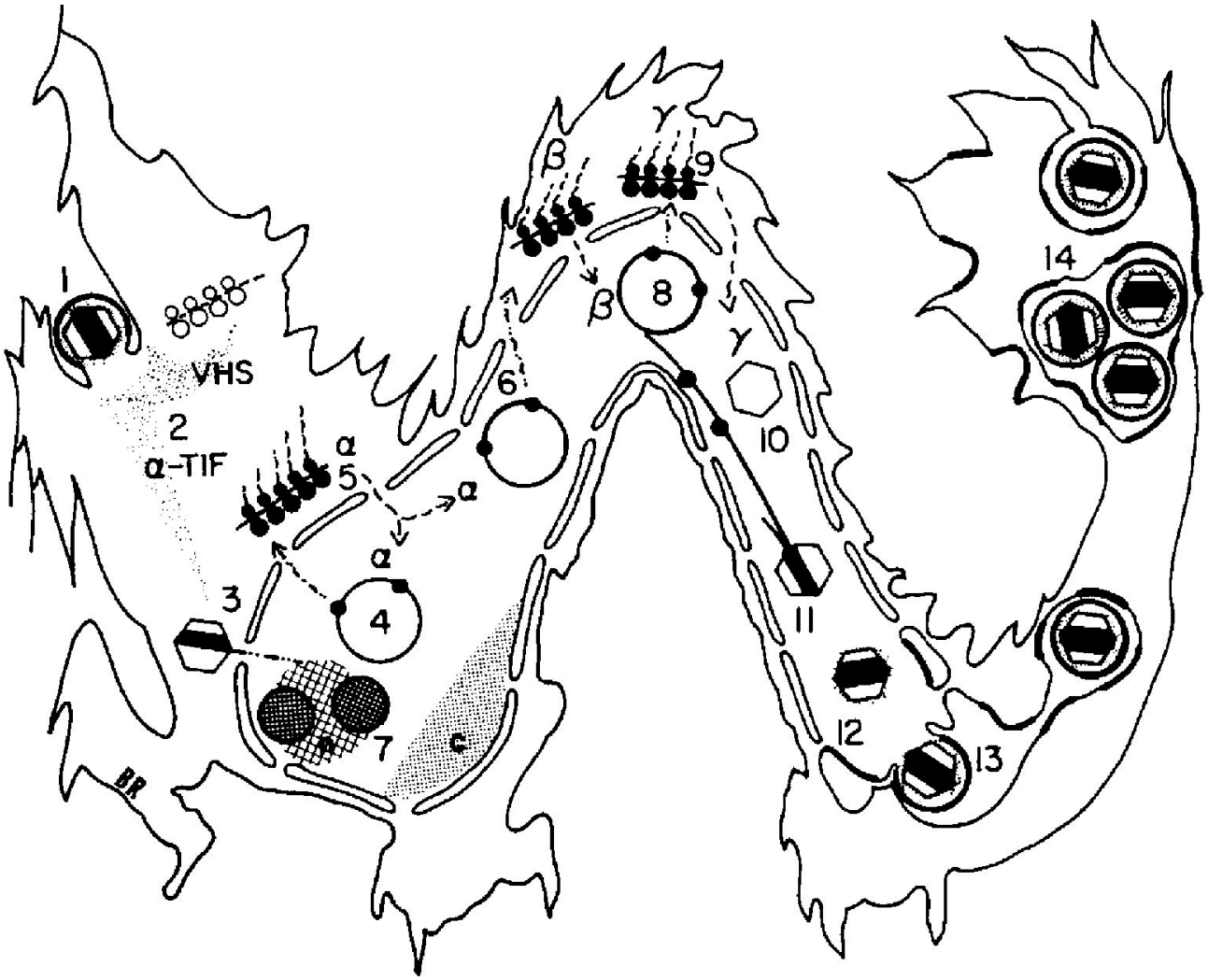
Миграция HHV-1 в инфекции *in vivo*



Вирус размножается в эпителиальных клетках(в месте первичного проникновения); затем перемещается по нейритам в нейроны, где осуществляется латентная инфекция

Цикл репликации вируса простого герпеса (HSV)

1: проникновение путем слияния оболочки с мембраной. **2**: VHS – блокировка синтеза клеточных белков; α-TIF (**α** gene frans-inducing factor) - транспорт в ядро. **3**: транспорт капсида в ядро, циклизация ДНК в нуклеоплазме. **4**: транскрипция α-генов клеточными ферментами; α-TIF - индуктор. **5**: трансляция 6 **α**-мРНК, транспорт белков в ядро. **6**: экспрессия **β**-генов. **7**: деградация хроматина (**c**) и ядрышка. **8**: репликация вирусной ДНК по механизму «катящееся кольцо» **9**: экспрессия **γ**-генов. **10**: образование пустых капсидов. **11**: паковка ДНК в капсиды. **12**: паковка белков в капсид. **13**: отпочковывание от внутренней ядерной мембраны **14**: белки оболочки аккумулируются на мембранах ЭПР



Избегание герпесвирусами иммуного ответа

Деградация клеточных рецепторов герпесвирусами

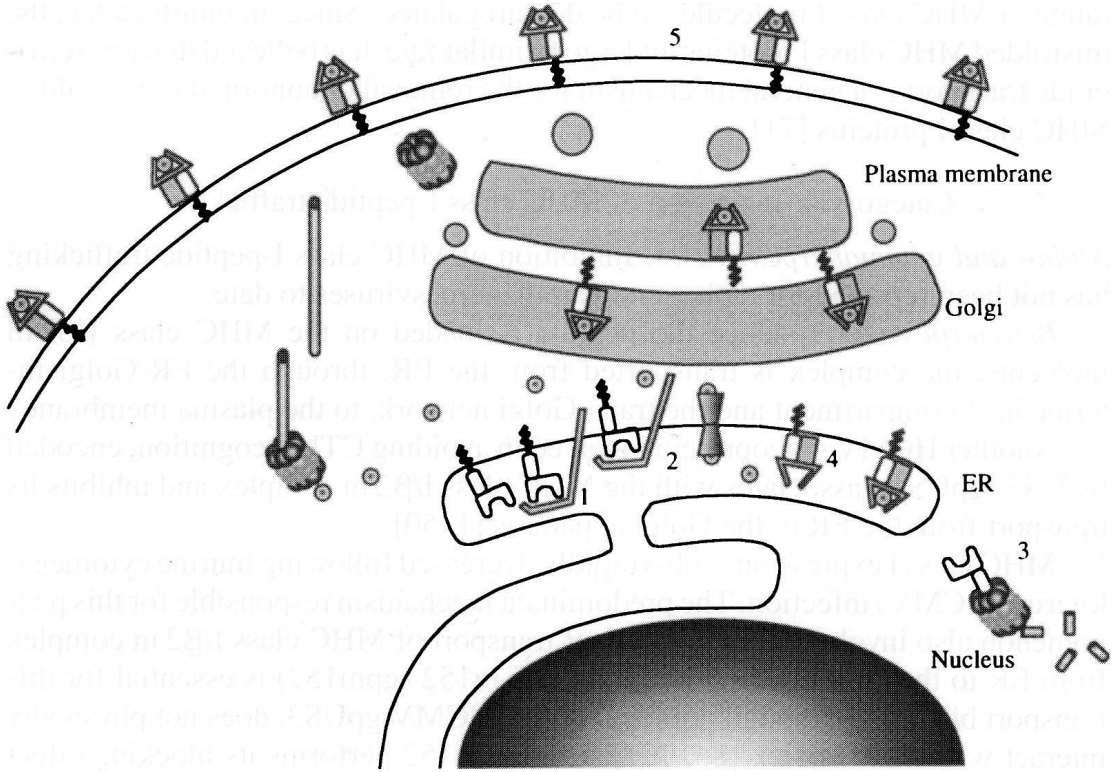


Fig. 8. HCMV abrogates MHC class I expression and induces the expression of a MHC class I homologue. In HCMV-infected cells, the US11 gene product (*1*) shunts nascent MHC class I proteins from the ER back into the cytosol (the HCMV US2 gene product does the same, albeit with both nascent and properly folded MHC class I molecules) (*2*), where it is rapidly degraded by the proteasome (*3*). MHC class I-peptide which was present on the cell surface before the action of US11/US2 are lost due to normal turnover. This loss of MHC class I-peptide on the cell surface renders the cell susceptible to the action of NK cells (cf. Fig. 6). However, the gene product of another HCMV gene, UL18 (*4*), has homology to MHC class I, binds both β2-microglobulin and peptide, and reaches the cell surface (*5*). This protein acts as a 'decoy', since it resembles MHC class I-peptide strong enough to inhibit NK cell activity, but not enough to activate CTLs ([5, 94 95], adapted from [98])

«Связывание» антител белками вируса простого герпеса

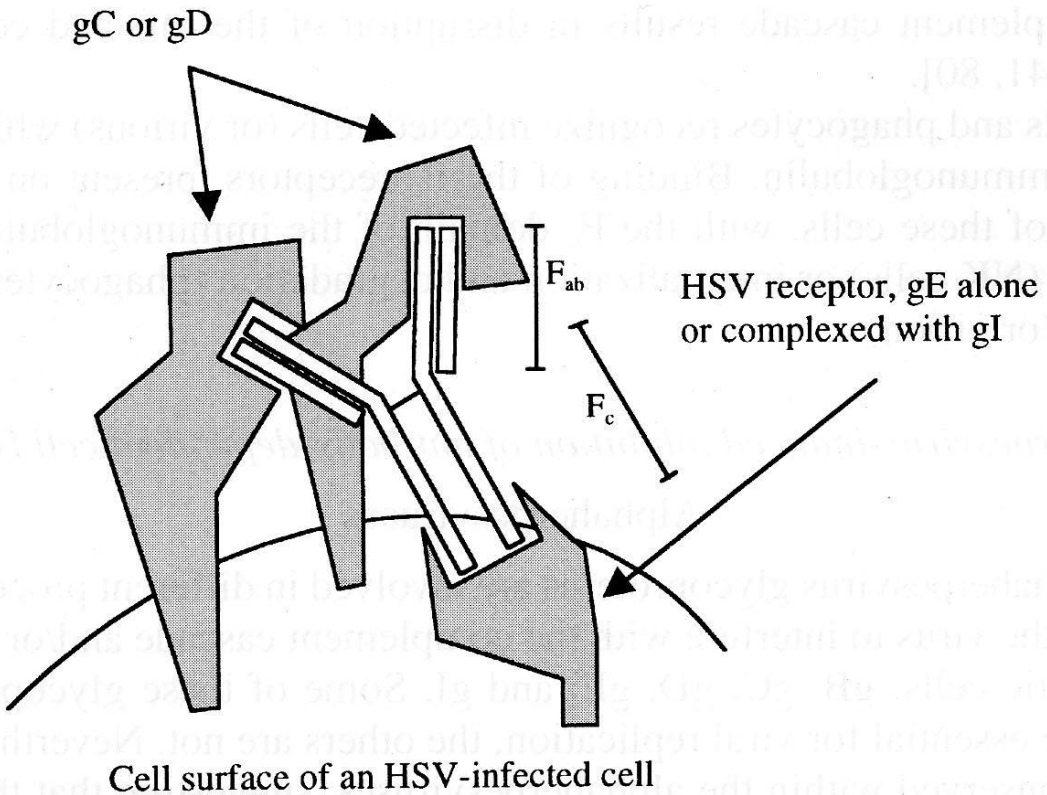


Fig. 2. Antibody bipolar bridging caused by the HSV gE-gI complex. Virus-specific antibodies bind with their F_{ab} domain to their respective ligand (viral glycoproteins which become expressed on the cell surface of the infected cell) and with their F_c domain to the gE-gI F_c receptor. Thereby, antibodies are unable to activate the classical complement pathway or activate phagocytes (adapted from [28])

Модификация клеточных рецепторов герпесвирусами

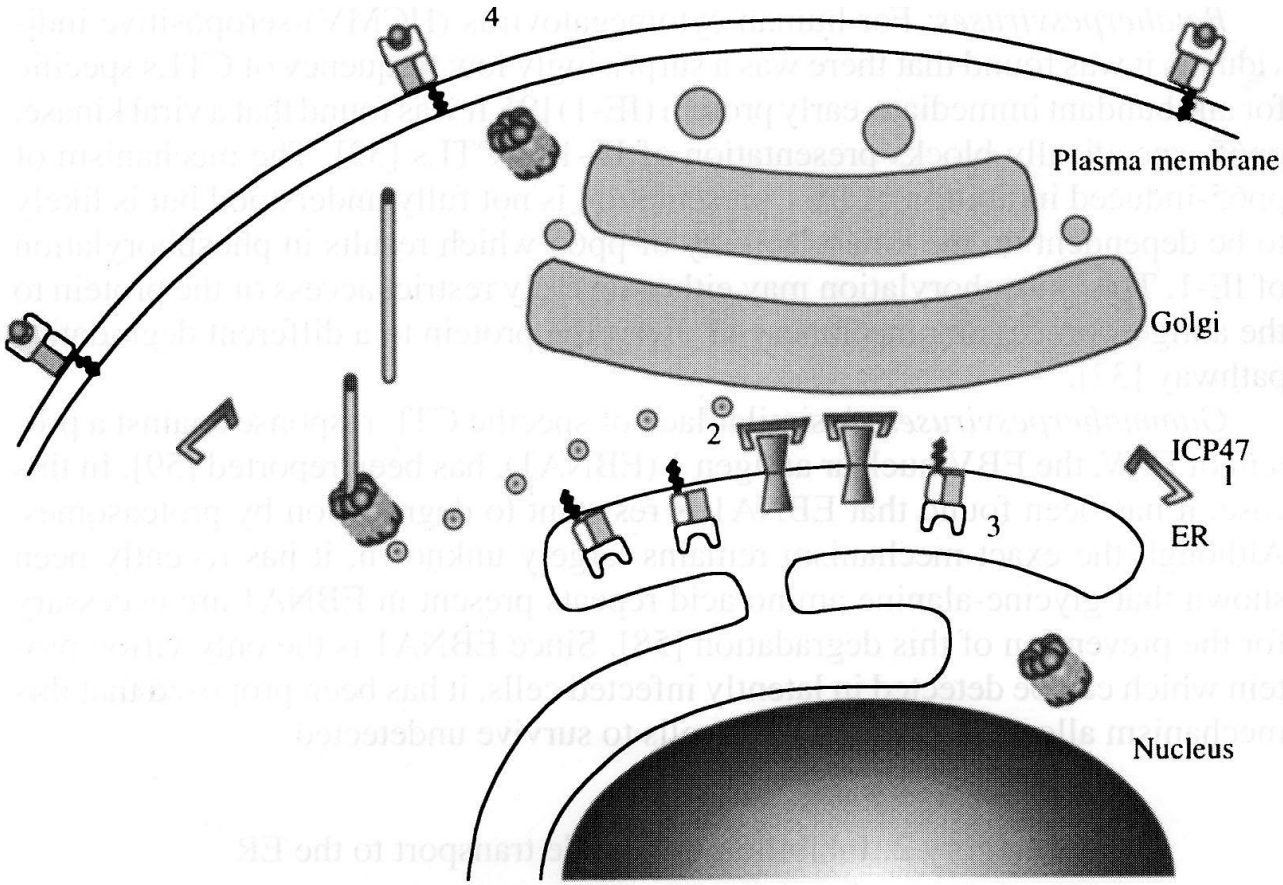
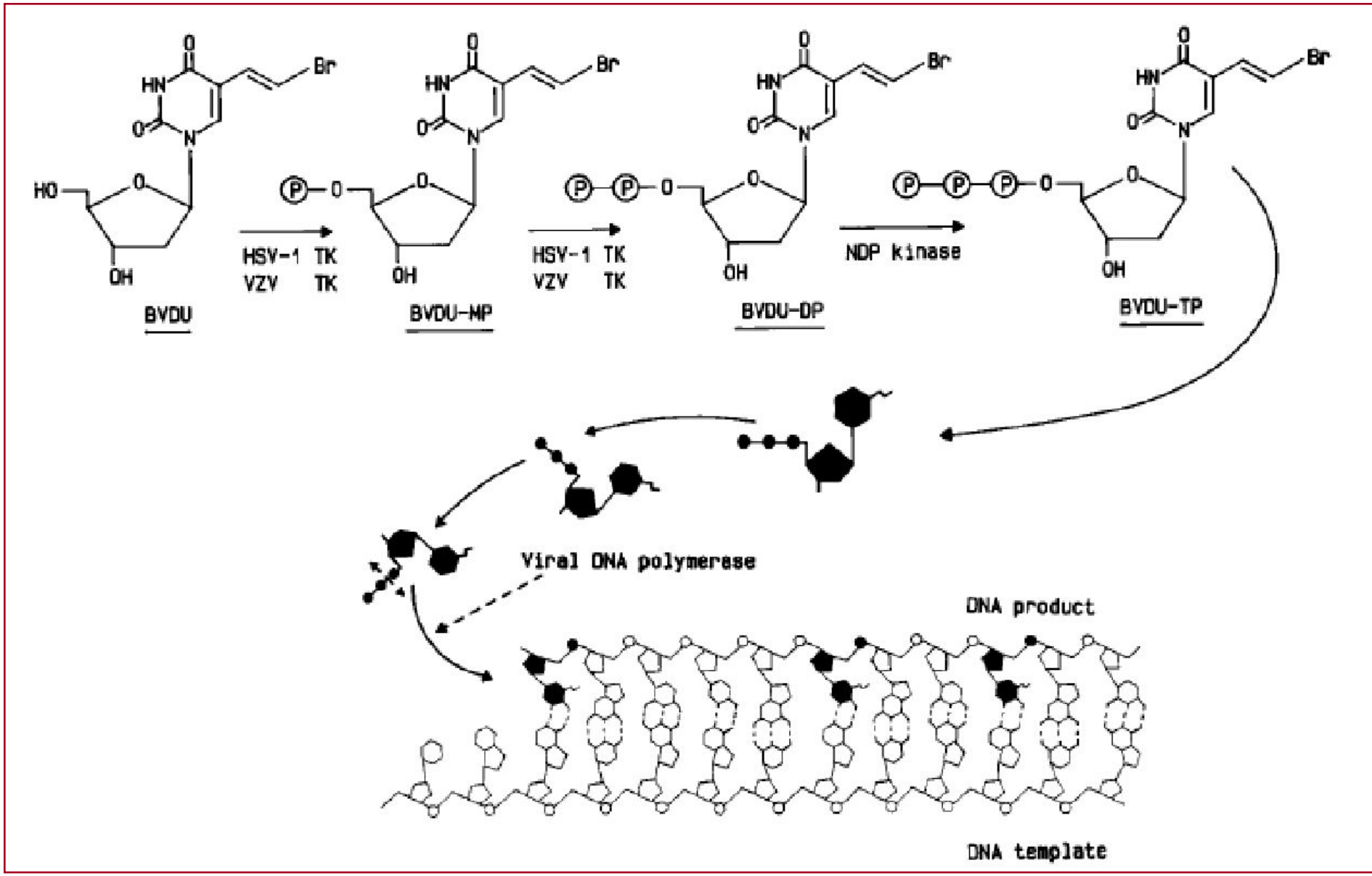


Fig. 7. HSV ICP47 inhibits antigen presentation by blocking TAP. In HSV-infected cells, the cytoplasmic ICP47 (*1*) binds to the cytoplasmic side of TAP (*2*), thereby blocking the peptide-binding site and preventing peptides from entering the ER lumen. Since MHC class I cannot exit the ER, unless it is complexed with a peptide, it is retained in the ER and no newly formed MHC class I (which could carry viral peptides) reaches the surface. Only MHC class I-peptide complexes formed prior to viral infection are present on the cell surface (*4*), and these are lost in time due to normal turnover ([40], adapted from [98])

Противогерпетические препараты

Механизм действия ацикловира и пр. производных



Poxviridae

линейная ds-ДНК 135 - 375 т.п.н.

Entomopoxvirinae: Alpha-, Betha- и Gammaentomopoxvirus

Chordopoxvirinae:

Avipoxvirus **(птицы),**

Capripoxvirus **(козы и овцы),**

Leporipoxvirus **(зайцы, кролик, белки)**

Molluscipoxvirus **(человек)**

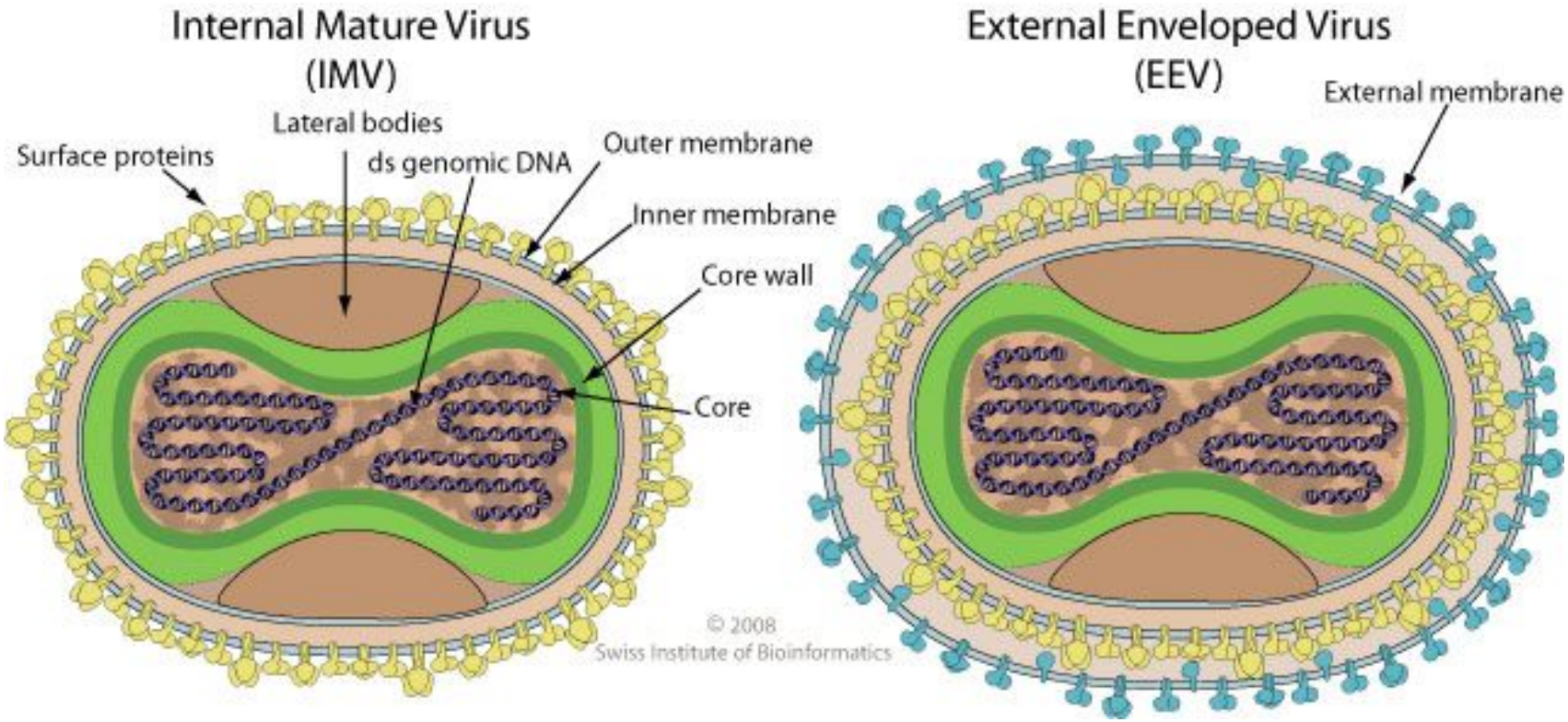
Orthopoxvirus **(животные и человек)**

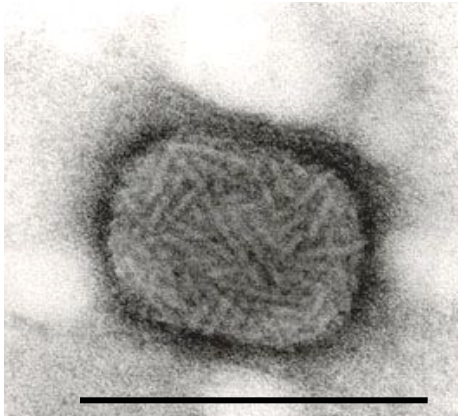
Parapoxvirus **(крупный рогатый скот, олени, белки, человек)**

Suipoxvirus **(свиньи),**

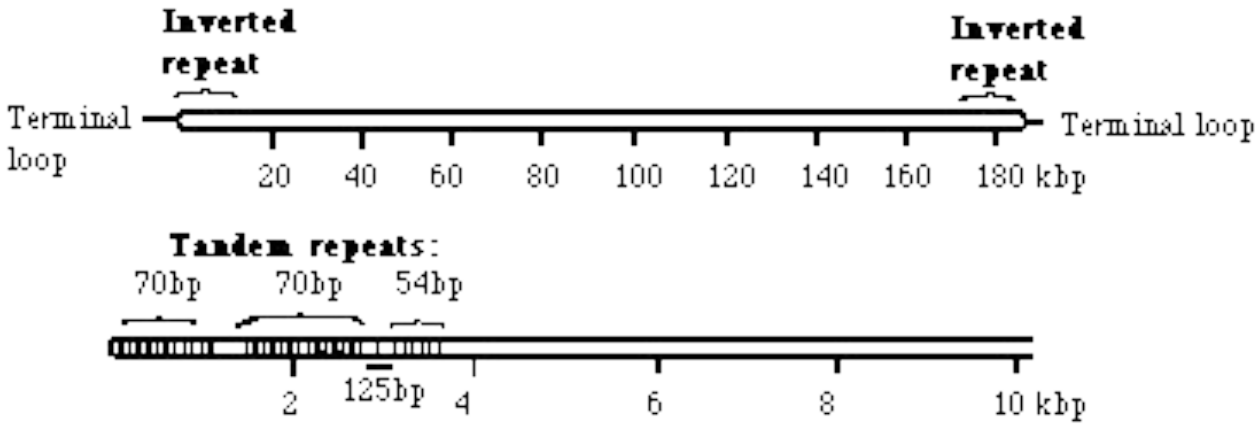
Yatapoxvirus **(обезьяны и человек).**

- Весь цикл размножения происходит в цитоплазме
- Все ферменты первичной транскрипции пакуются в вирионы
- Геном кодирует все ферменты репликации ДНК
- Существует два типа инфекционных частиц
- Выход из хозяйской клетки может осуществляться различными способами
- Заболевания человека имеют характерную симптоматику


Internal Mature Virus
(IMV)
Lateral bodies
Surface proteins
ds genomic DNA
Outer membrane
Inner membrane
Core wall
Core
© 2008
Swiss Institute of Bioinformatics
External Enveloped Virus
(EEV)
External membrane



300нм


Inverted repeat
Inverted repeat
Terminal loop
Terminal loop
20
40
60
80
100
120
140
160
180 kbp
Tandem repeats:
70bp
70bp
54bp
125bp
2
4
6
8
10 kbp

1 Entry
Intracellular mature virion (IMV) particles bind to unknown receptor(s) and fuse with the cell membrane. Extracellular enveloped virion (EEV) particles bind to unknown receptor(s) and are endocytosed into the cell.

2 Initial Uncoating
The viral core particle (CORE) containing the viral genome, the viral DNA-dependent RNA polymerase, and other enzymes is released into the cytoplasm.

3 Early Transcription
Early genes (including those coding for immunomodulatory proteins, enzymes, and replication and transcription factors) are transcribed and translated immediately upon core particle entry into the cytoplasm of the cell.

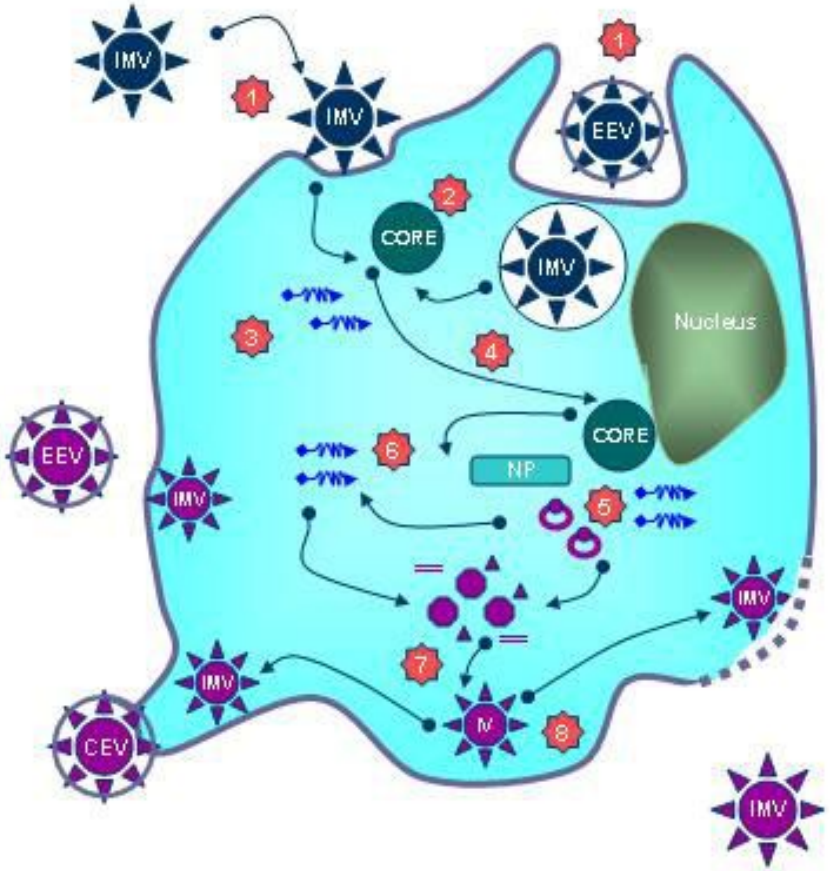
4 Translocation
The viral core particle translocates to the outside of the cell nucleus.

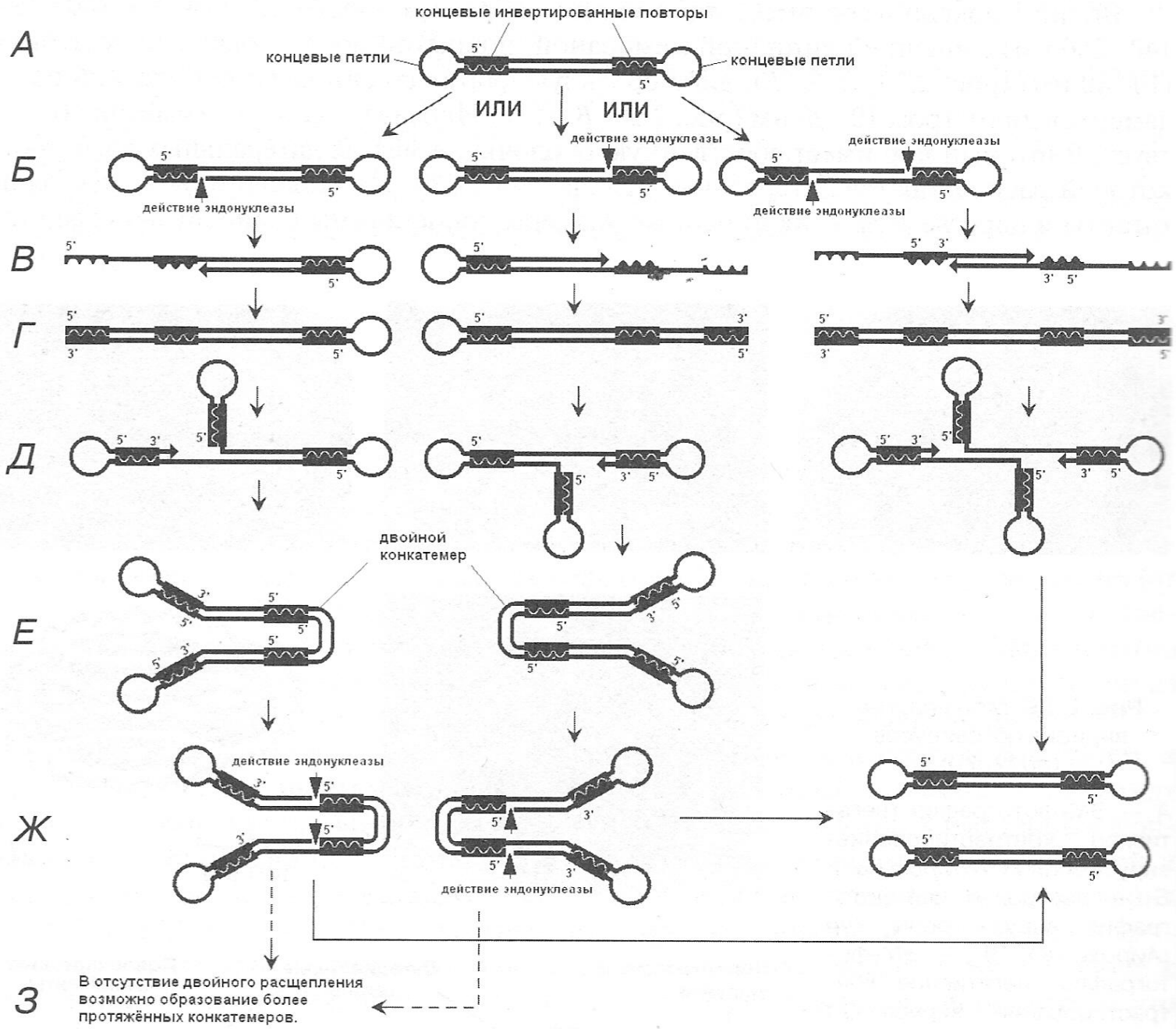
5 Secondary Uncoating
The viral nucleoprotein (NP) complex is released containing the viral genome. At this point the viral genome is replicated as a concatemer and transcription and translation of intermediate genes (mainly coding for transcription factors) occurs.

6 Late Transcription
The viral late genes (coding for structural proteins, enzymes and transcription factors) are transcribed And translated.

7 Assembly
Concatemeric intermediates are resolved into linear double stranded DNA and packaged with late viral proteins into immature virions (IV).

8 Release
IV's mature into IMV's via an undescribed mechanism which May include processing of the IV through the Golgi apparatus. The IMV's are transported to the periphery of the cell where they are released in one of three ways. IMV's released via cell lysis remain IMV's. Alternatively, IMV's can bud through to the cell surface, picking up a viral envelope from the cell plasma membrane. On the surface these cell-associated enveloped Virions (CEV's) are pushed via an Actin tail into contact with a second cell. Lastly the IMV can bud through the plasma membrane picking up an envelope and becoming an EEV.




А
концевые инвертированные повторы
концевые петли
концевые петли
или
или
Б
действие эндонуклеазы
действие эндонуклеазы
действие эндонуклеазы
В
Г
Д
двойной конкатемер
Е
действие эндонуклеазы
Ж
действие эндонуклеазы
З
В отсутствие двойного расщепления возможно образование более протяжённых конкатемеров.

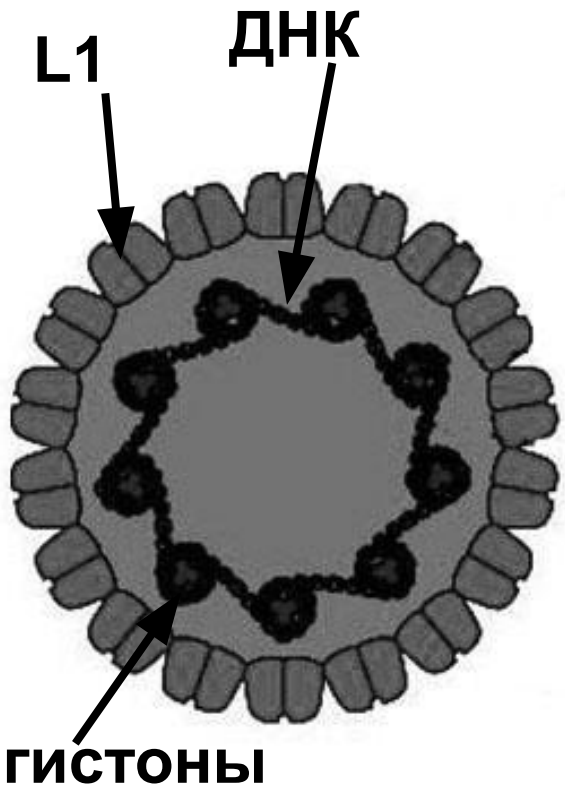
Papillomaviridae

кольцевая ds-ДНК 7 - 8 т.п.н.

16 родов (млекопитающие, птицы, холоднокровные)

Alphapapillomavirus инфицируют преимущественно оральный и урогенитальный эпителий людей и приматов

Betapapillomavirus инфицируют преимущественно кожные покровы человека

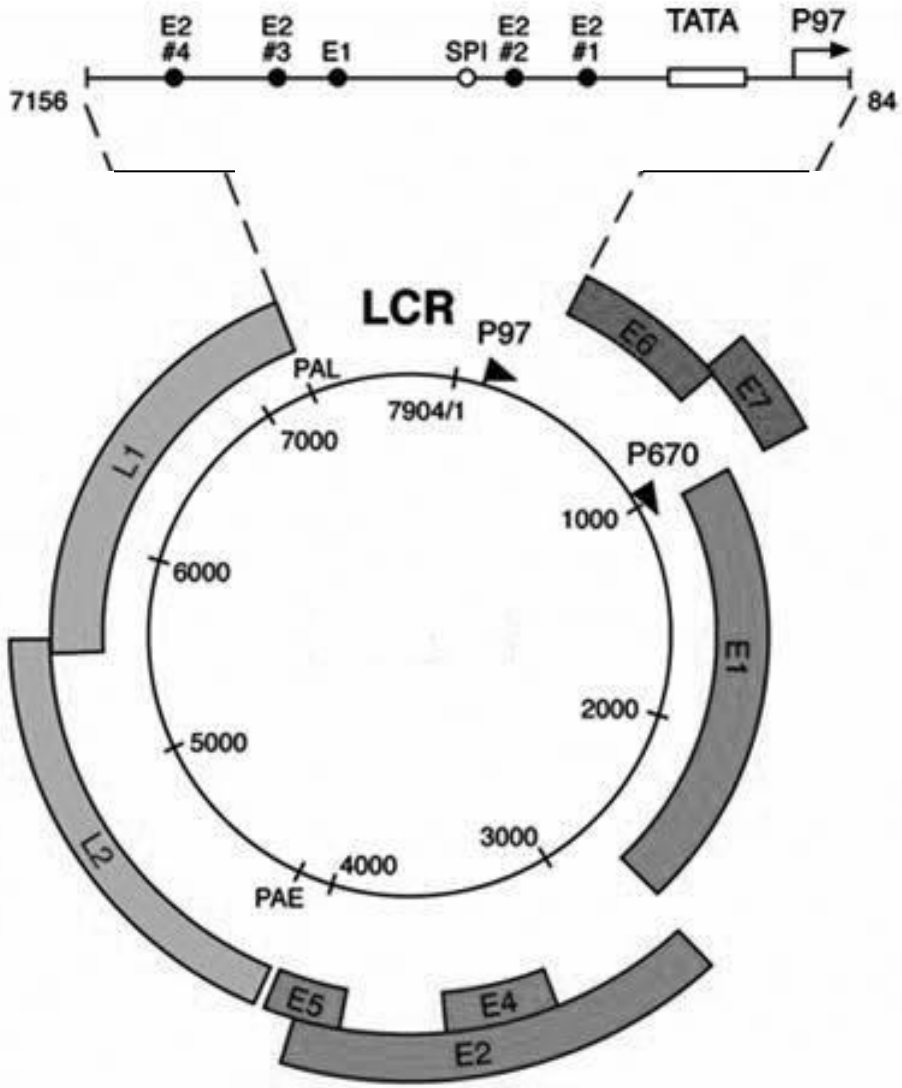


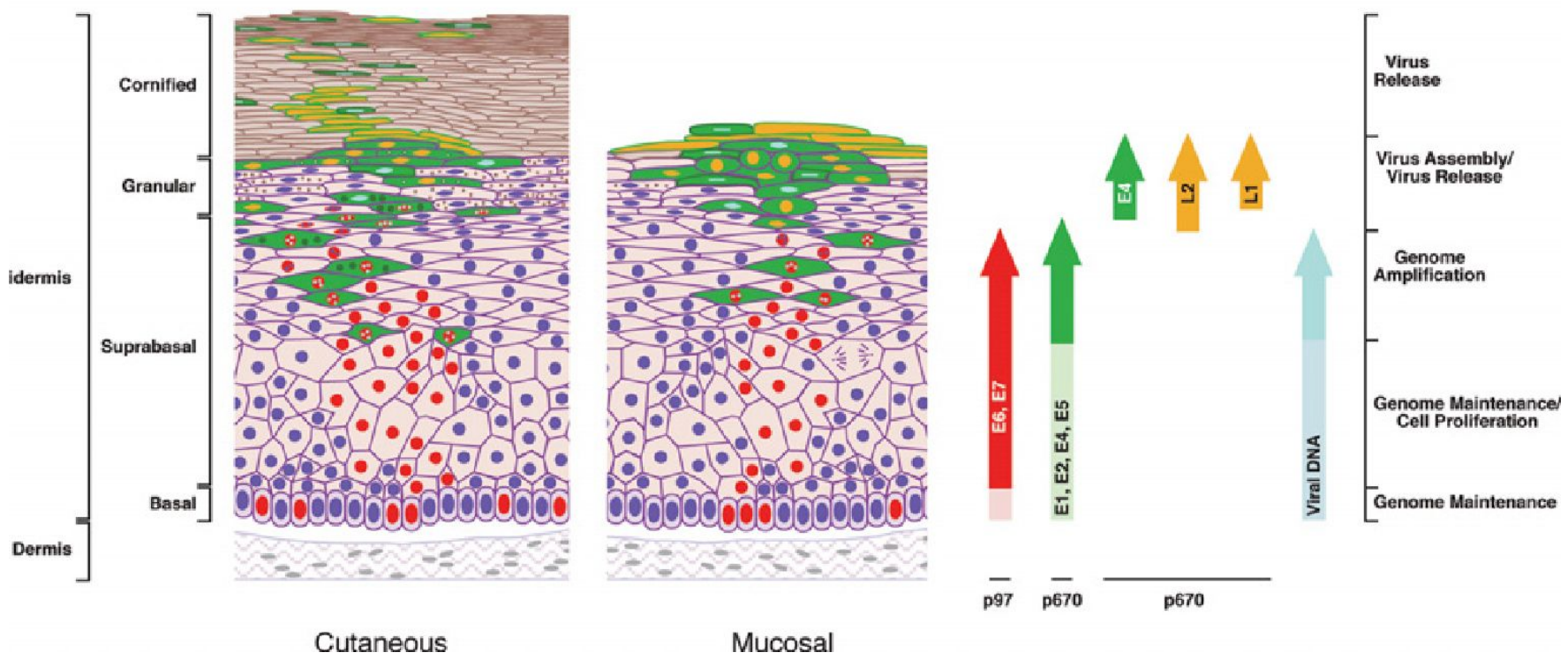
Зависят от ферментативного аппарата хозяина

Весь цикл размножения (включая сборку) происходит в ядре

Выраженный тканевой тропизм (базальный слой эпителия)

Осуществляют литическую инфекцию и способны к персистенции (в виде провируса или эписомы)


E2
#4
E2
#3
E1
SPI
E2
#2
E2
#1
TATA
P97
7156
84
LCR
P97
PAL
7904/1
7000
P670
1000
6000
2000
5000
3000
4000
PAE
L1
L2
E6
E7
E1
E5
E4
E2



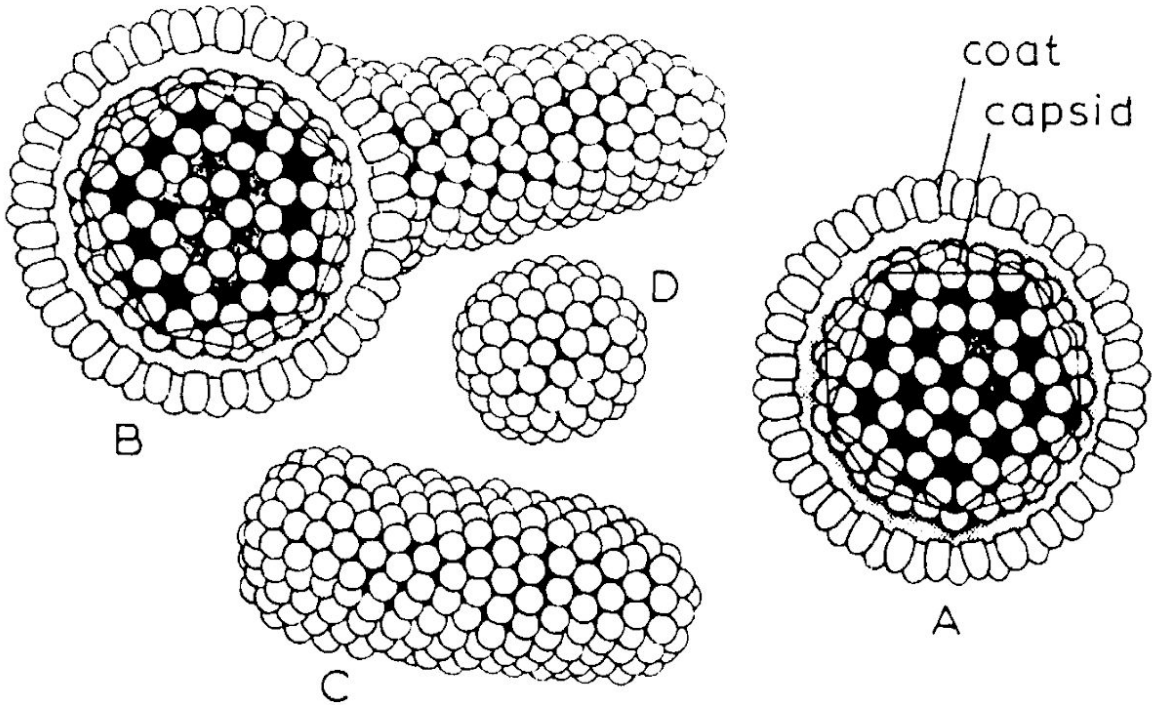
Изменения в эпителии в ходе инфекции.
Красные ядра – пролиферативные клетки. В результате инфекции они появляются в верхних слоях; вирусные белки E6 и E7 нарушают контроль дифференциации.
Зеленые клетки, красные ядра – экспрессия E6 и E7, активация p670 в верхних слоях эпителия; экспрессия L1 и L2; клетки содержат амплифицированную вирусную ДНК.
. **Зеленые клетки, желтые ядра** –клетки содержат инфекционные частицы

F. Hepadnaviridae

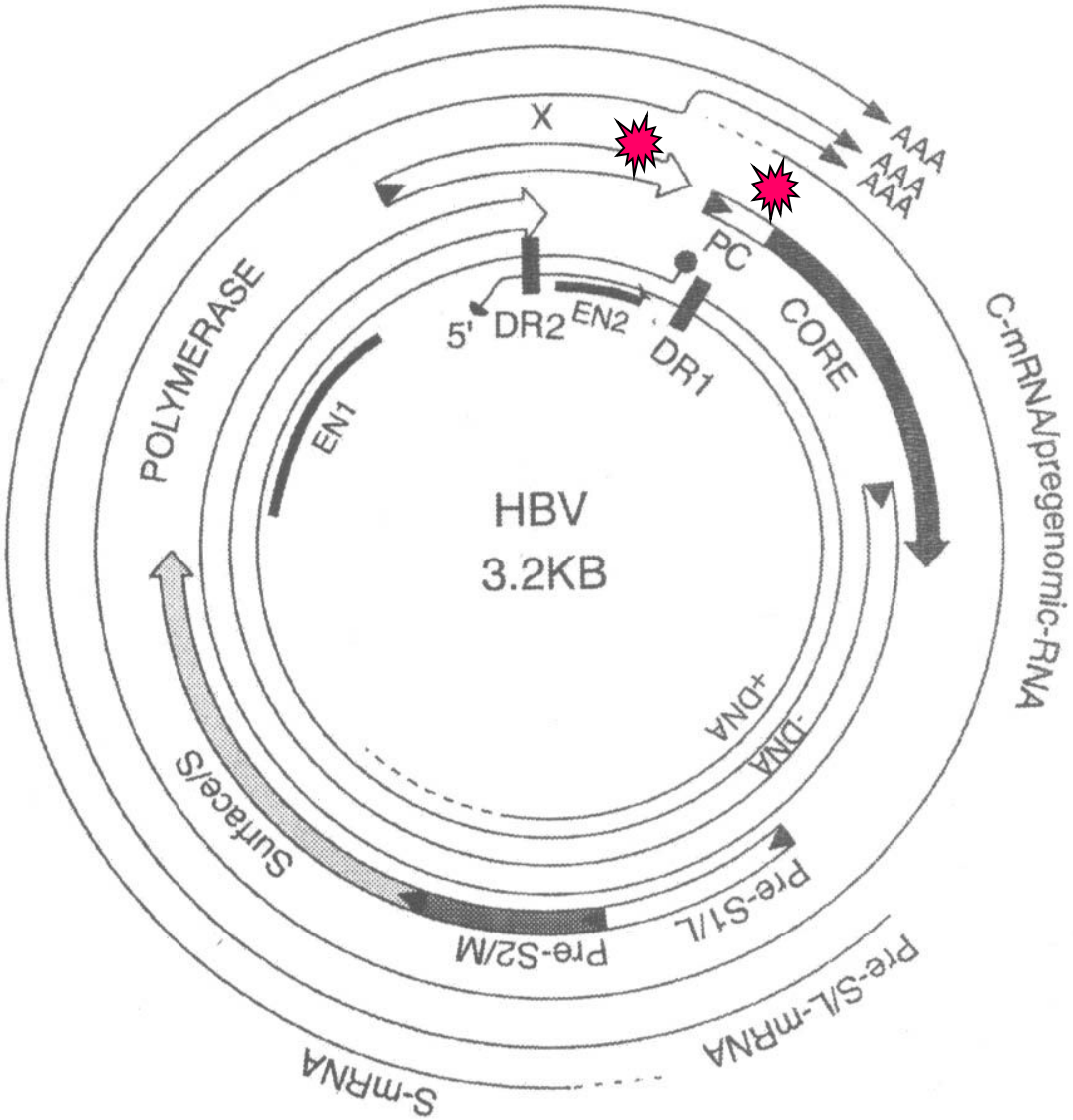
- G. Avihepadnavirus. Гепатит В- подобные вирусы пекинской утки, цапли и пр.
- G. Orthohepadnavirus. **Гепатит В человека**, вирус земляной белки, вирус сурка

Строение вирионов HBV

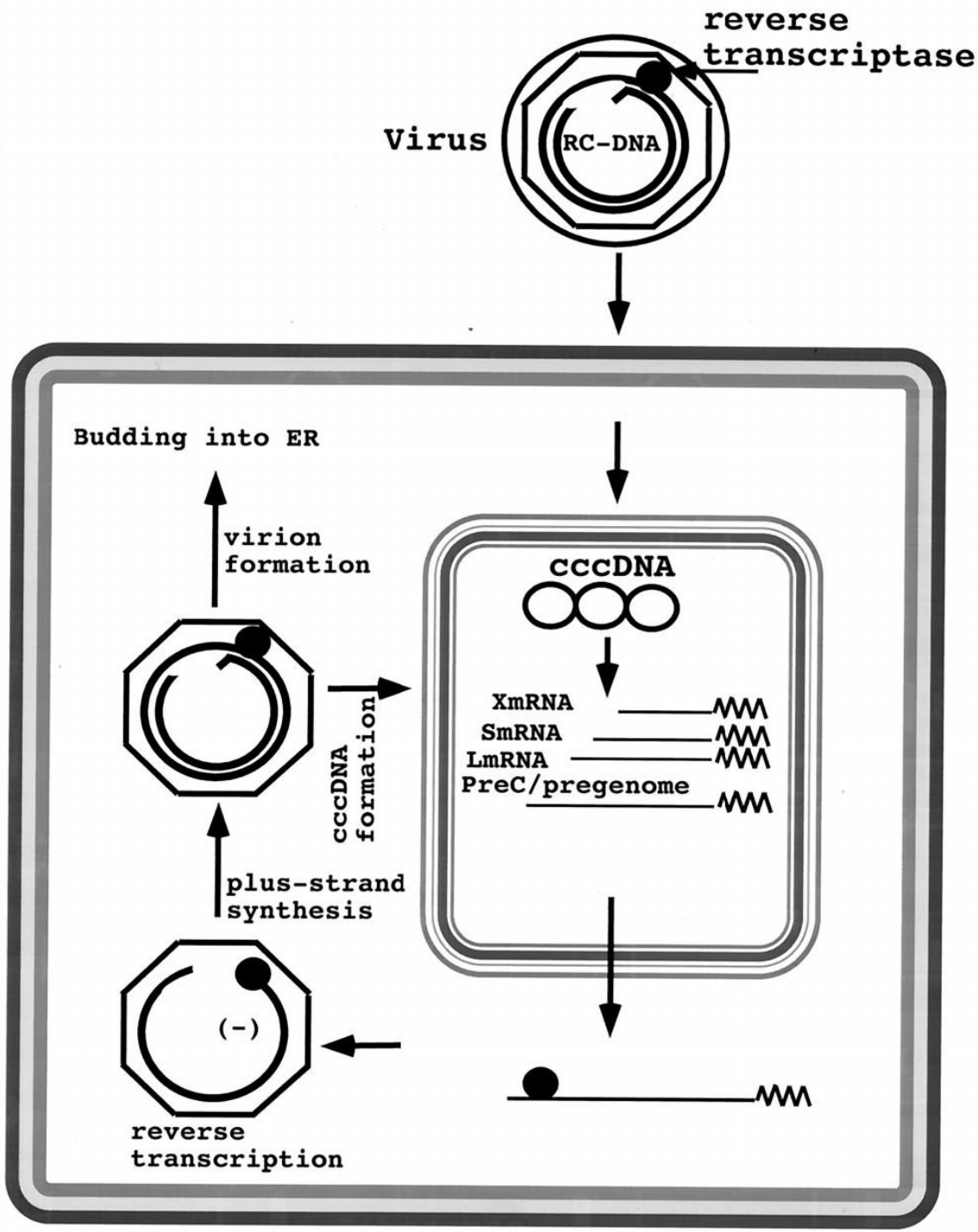
Human hepatitis B virus and associated structures



A. Normal isometric virus with icosahedral capsid or "core" surrounded by a coat of HBsAg. B. Tadpole-shaped virus with elongated coat. C and D. Filamentous and spherical assemblies of excess coat protein. (From Stannard, L.M., *Animal Virus Structure*, Nermut, M.V. and Steven, A.C., Eds., Elsevier, Amsterdam, 1987, 361. With permission.)

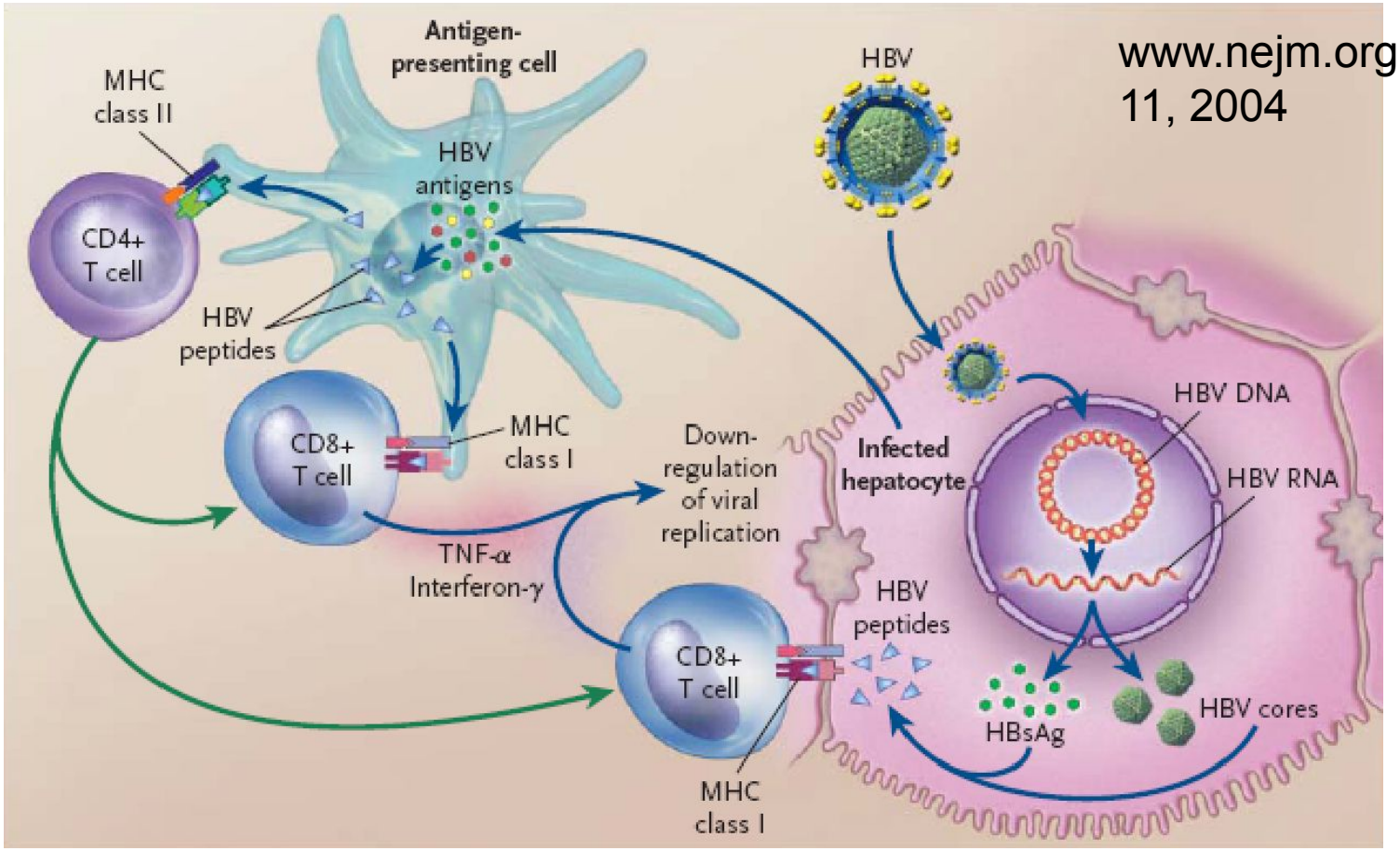


Физическая карта генома HBV



Цикл репликации вируса гепатита В (HBV)

Cellular Immune Responses to HBV.



www.nejm.org march 11, 2004

HBV replicates in hepatocytes to produce HBsAg particles and virions. Both types of particle can be taken up by antigenpresenting cells, which degrade the viral proteins to peptides that are then presented on the cell surface bound to MHC class I or II molecules. (Antigen-presenting cells can also process and display viral antigens taken up by phagocytosis of killed infected hepatocytes.) These peptide antigens can be recognized by CD8+ or CD4+ T cells, respectively, which are thereby sensitized. Virus-specific CD8+ cytotoxic T cells (with help from CD4+ T cells, green arrow) can recognize viral antigens presented on MHC class I chains on infected hepatocytes. This recognition reaction can lead to either direct lysis of the infected hepatocyte or the release of interferon *g* and TNF*a* , which can down-regulate viral replication in surrounding hepatocytes without direct cell killing.

Гепатит Дельта – спутник HBV

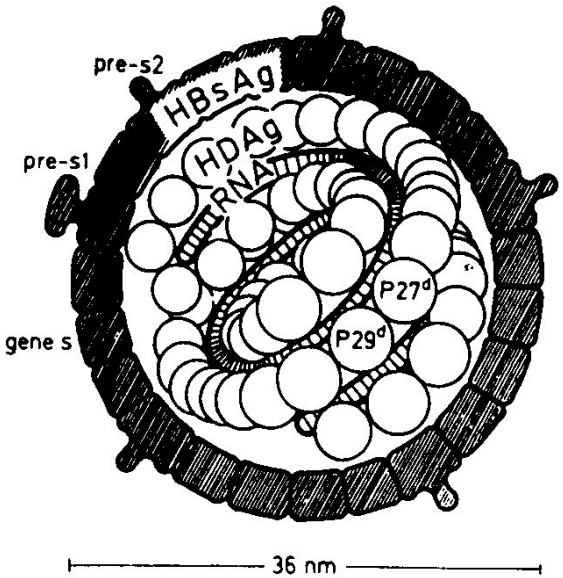


FIGURE 206

Deltavirus of hepatitis D. A defective virus that needs the presence of hepatitis B virus for replication and borrows its envelope from this agent. Hepatitis delta antigen (HDAg) is an internal component of the virus and consists of two proteins (P27, P29). The envelope contains S and pre-S polypeptides of hepatitis B virus. (From Zyzik, E., Ponsetto, A., Forzani, B., Hele, C., Heermann, K.-H., and Gerlich, W.H., *Hepadna Viruses,* Robinson, W., Koike, K., and Will, H., Eds., Alan R. Liss, New York, 1987, 565. With permission.)

Геном HDV

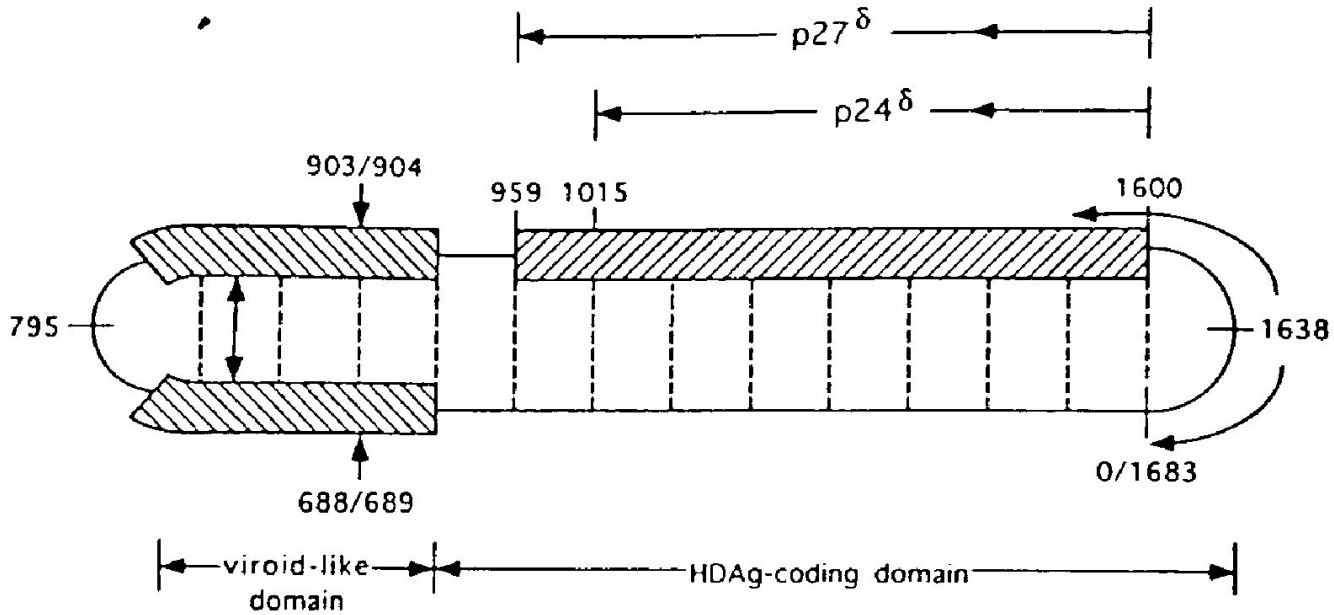
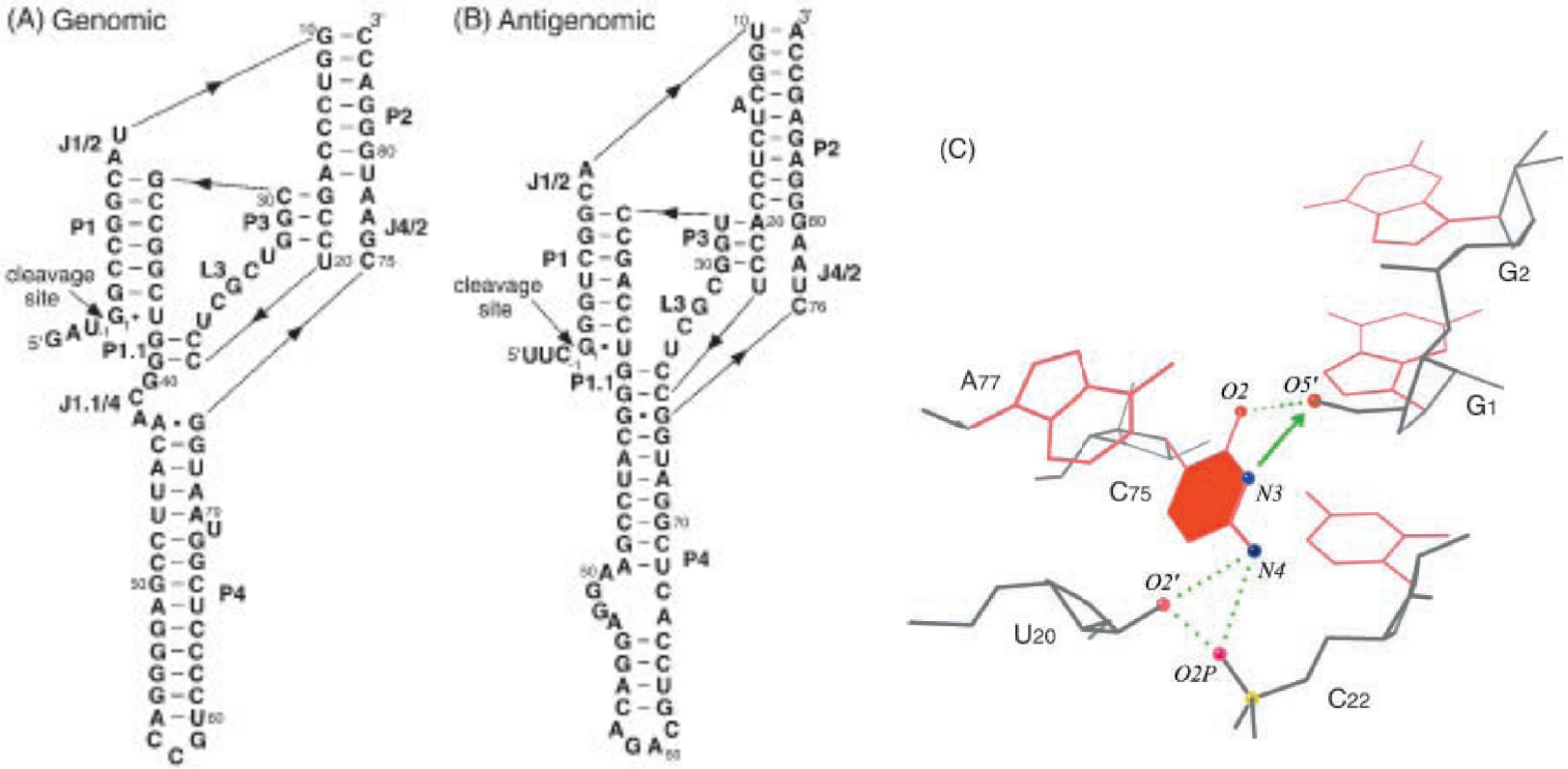


Figure 1 Genomic organization of the hepatitis D virus. The direction of the genomic sense RNA sequence is clockwise. The HDAg coding region is on the antigenomic strand. Dashed lines indicate complementary sequences. (From Ref. 9.)

Replication of the HDV RNAs is performed by the host cell RNA polymerase II.

Genomic (*A*) and antigenomic (*B*) HDV ribozymes